UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,037	07/23/2003	Warren J. Scherer	512-160	1255

7590 03/11/2009

Ronald J. Baron, Esq.
HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
03/11/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,037	SCHERER, WARREN J.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,11,12 and 34-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2,11-12 and 34-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09 Dec 08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2, 11-12 and 34-36 are presented for examination.

Applicant's Amendment and Information Disclosure Statement (IDS) filed December 9, 2008 have each been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08a (two pages total), the Examiner has considered the cited references.

Claims 1-2, 11-12 and 34-36 remain pending and under examination. Claims 1 and 36 are amended.

Applicant's arguments, filed December 9, 2008, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 11-12 and 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wymenga et al. ("Management of Hot Flushes in Breast Cancer Patients", *Acta Oncologia*, 41(3); 2002:269-275) in view of Gil et al. (U.S. Patent Application Publication No. 2003/0229088; Issued December 2003, Filed May 2002), Burke et al. ("Preclinical Evaluation of Brimonidine", *Survey of Ophthalmology,* 41(Supp.1), 1996; S9-S18) and Dictionary.com ("Topical" and "Transdermal", 2008), each already of record, for the reasons of record set forth at p.5-13 of the previous Office Action dated June 10, 2008, of which said reasons are herein incorporated by reference.

Newly amended claims 1 and 35, which now require that the composition is topically administered "locally" to the skin of the human and that the selective alpha-2 adrenergic receptor agonist acts locally, remain properly included in the rejection because Wymenga et al. teaches the treatment of menopausal symptoms, such as hot flashes, with clonidine, a centrally active alpha-adrenergic agonist that reduces vascular reactivity, in low dosages that were demonstrated to be effective in the reduction of hot flushes caused by normal menopause either when administered orally or transdermally (abstract; col.2, para.2, p.269; col.2, para.4, p.271).

Regarding Applicant's limitation directed to topical administration "locally to the skin of the human" (claim 1) or "locally to the facial skin" (claim 35), Wymenga et al. teaches the transdermal application of the alpha-adrenergic agonist to reduce the incidence of hot flushes in menopausal women. The teaching and suggestion of transdermal application of the alpha-adrenergic agonist is considered to meet Applicant's limitation directed to topical administration because, as evidenced by Dictionary.com, transdermal is defined as "applied to the skin, usually as part of an adhesive patch for absorption into the bloodstream" and topical is defined as "of, pertaining to, or applied externally to a particular part of the body". In view of such teachings, the fact that transdermal administration necessarily means application directly to the skin clearly meets the requirements of "topical" administration as instantly claimed, which is defined in the art as application externally to a particular part of the body (i.e., in this case, the skin organ). Furthermore, since transdermal application does result in absorption of the active agent into the bloodstream, the active agent would be distributed throughout the body via the bloodstream and, thus, would act "locally" at the site of the facial flushing to exert its selective alpha-adrenergic receptor agonist activity once it was distributed to this site of the skin (as required by instant claim 1 and claim 35, wherein the brimonidine compound acts "locally"), absent factual evidence to the contrary. As a result, the teaching and suggestion to apply an alpha-adrenergic agonist transdermally to the skin clearly meets Applicant's claimed limitation directed to topical administration "locally to the skin of the human" (claim

1) or "locally to the facial skin" (claim 35), since transdermal administration necessarily circumscribes external application directly to the skin, absent factual evidence to the contrary.

It is also again clarified for the record that Applicant has failed to provide any *explicit definition* of the term "topically administering" in the instant specification so as to direct the interpretation of the term for examination. Accordingly, in the absence of a definition for the term "topically administering", the Examiner defaults to the broadest, most reasonable interpretation of this term consistent with the art to claims in accordance with the MPEP at §2111 and, therefore, relies upon the cited dictionary reference as described *supra* for the art-accepted meaning of the terms.

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that brimonidine and clonidine are not functionally equivalent for a given condition because, as taught by Arndt et al. (filed on Applicant's IDS), clonidine may be used for treating menopause-related flushing, but is apparently ineffective in rosacea. By contrast, Applicant states that brimonidine is effective for reducing flushing due to rosacea and, therefore, it is clear that a given alpha-adrenergic agonist useful in reducing redness caused by one condition is not necessarily useful in reducing redness caused by another condition. Secondly, Applicant argues that the fact that both brimonidine and clonidine are useful in alleviating pain does not suggest that either is necessarily useful for treating menopause-associated hot flashes. Thirdly, Applicant argues that transdermal administration of a drug is not the same as topical administration of the same. Applicant insists that transdermal administration is a form of systemic administration, whereas topical administration is a means of local administration. Applicant further alleges that the specification requires that the agonist be applied such that it acts locally and, thus, clearly excludes transdermal administration by requiring that the agonist acts locally.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Firstly, Applicant's arguments that clonidine and brimonidine would not be functionally equivalent for treating menopause-associated hot flushes because alpha-adrenergic agonists useful in reducing redness from one condition are not necessarily useful in reducing redness caused by another condition is unpersuasive. The prior art at the time of the instant invention clearly and explicitly acknowledged that the two compounds (i.e., clonidine and brimonidine) share the same overall function as alpha-adrenergic agonist and, thus, are "functionally equivalent" for this purpose. The very fact that the two compounds may exhibit differing function in treating, e.g., redness associated with rosacea (i.e., that clonidine is ineffective for treating redness due to rosacea, while brimonidine is apparently effective for treating the same), does not negate this clear teaching that the two compounds fundamentally act as agonists of alpha-adrenoreceptors, wherein, according to Wymenga et al., agonism at such alpha-adrenoreceptors is effective for reducing facial flushing resulting from menopause-associated hot flashes. In fact, one of ordinary skill in the art would have reasonably expected that the function of the two compounds in treating other various disorders (particularly disorders that have not been explicitly demonstrated to be associated with, or treatable via modulation of, alpha-adrenoreceptors), even other disorders associated with redness and flushing, would have differed between the two compounds due to the chemical and structural differences between the two compounds. Accordingly, Applicant's allegation that clonidine and brimonidine must not be functionally equivalent to one another on the grounds that they do not share the same activity in treating redness associated with flushing due to rosacea is unpersuasive because, while the efficacy in treating redness associated with flushing due to rosacea may very well differ between the two compounds, the fact remains that Wymenga et al. clearly teaches the efficacy in agonizing the alpha-adrenoreceptor to reduce the incidence of menopause-associated hot flashes and, therefore, also clearly suggests that the use of another compound with the same function in agonizing alpha-adrenoreceptors (i.e., in this case, brimonidine tartrate as disclosed by Gil et al.) would

have been reasonably expected to achieve this same therapeutic effect as the clonidine compound used in Wymenga et al., absent factual evidence to the contrary.

Secondly, Applicant's argument that the fact that both brimonidine and clonidine are useful in alleviating pain does not suggest that either is necessarily useful for treating menopause-associated hot flashes is also unpersuasive. This argument appears to find its alleged support in the fact that Gil et al. discloses brimonidine and clonidine as functionally interchangeable for the treatment of pain. Such an argument, however, appears to ignore the very fact that Gil et al. *further discloses that brimonidine and clonidine and functionally equivalent in their activity as alpha-adrenergic agonists.* Thus, aside from whatever equivalent efficacy the two compounds may have in alleviating pain, the two compounds are taught in the prior art as both being capable of operating to agonize the alpha-adrenergic receptor. These facts, coupled with the teaching of Wymenga et al. that agonizing the alpha-adrenoreceptor using an alpha-adrenergic agonist such as clonidine is effective to reduce hot flushes caused by normal menopause, provides at least a reasonable expectation of success that another compound functional to agonize this same alpha-adrenoreceptor would have the same efficacy in also reducing hot flushes caused by normal menopause, absent factual evidence to the contrary. This expectation is unrelated to its efficacy in alleviating pain as alleged by Applicant. Applicant is reminded that rejections under 35 U.S.C. 103(a) require at least a reasonable expectation of success, but not *absolute predictability.* Please see MPEP §2143.02, "The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co. Inc.,* 800 F.2d 1091, 231 USPQ 375 (Fed.Cir. 1986)...***Obviousness does not require absolute predictability, however, at least some degree of predictability is required.***"

Thirdly, and lastly, Applicant's argument that transdermal administration as taught by the cited prior art is note the same as topical administration as instantly claimed is, again, unpersuasive. Wymenga et al. teaches the transdermal application of the alpha-adrenergic agonist to reduce the incidence of hot

flushes in menopausal women. As explained in previous Office Actions and again herein, the teaching and suggestion of transdermal application of the alpha-adrenergic agonist is considered to meet Applicant's limitation directed to topical administration because, as evidenced by Dictionary.com, transdermal is defined as "applied to the skin, usually as part of an adhesive patch for absorption into the bloodstream" and topical is defined as "of, pertaining to, or applied externally to a particular part of the body". In view of such teachings, the fact that transdermal administration necessarily means application directly to the skin clearly meets the requirements of "topical" administration as instantly claimed, which is defined in the art as application externally to a particular part of the body (i.e., in this case, the skin organ).

Applicant attempts to further distinguish the instant claims over the cited prior art by amending the claims to require that the agonist "act locally" and by alleging that transdermal administration is a form of systemic administration, whereas topical administration is a means of local administration, and emphasizing that the specification apparently requires that the agonist be applied such that it acts locally. This also is, again, unpersuasive because transdermal application results in absorption of the active agent into the bloodstream and, thus, distributes the agent throughout the body via the blood. This same distribution throughout the body as a whole clearly supports the interpretation that the agent would act "locally", as instantly claimed, at the site of the facial flushing to exert its selective alpha-adrenergic receptor agonist activity once it has been distributed to this site of the skin via the bloodstream, absent factual evidence to the contrary. Accordingly, though Applicant appears to be of the persuasion that the newly added limitations directed to the agonist acting "locally" distinguish the instant claims over Wymenga et al. because the transdermal application as taught by Wymenga et al. does not act "locally", this is clearly erroneous because, for the reasons described *supra*, transdermal application as in Wymenga et al. does, in fact, have a local effect and, thus, meets both the requirements of the instant claims and the alleged requirement in the instant specification that the agonist be functional to act "locally". As a result,

the teaching and suggestion to apply an alpha-adrenergic agonist transdermally to the skin clearly meets Applicant's claimed limitation directed to topical administration "locally to the skin of the human" (claim 1) or "locally to the facial skin" (claim 35), since transdermal administration necessarily circumscribes external application directly to the skin and will have a "local" effect once distributed to the site of the facial flushing via the bloodstream, absent factual evidence to the contrary.

For these reasons *supra*, and those previously made of record at p.5-13 of the Office Action dated June 10, 2008, rejection of claims 1-2, 11-12 and 34-36 is proper.

Conclusion

Rejection of claims 1-2, 11-12 and 34-36 is proper.

No claims of the present application are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

March 6, 2009

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614